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Review article

Influence of cyclosporine on the occurrence of nephrotoxicity after allogeneic hematopoietic stem cell transplantation: a systematic review

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ABSTRACT

Cyclosporine, a drug used in immunosuppression protocols for hematopoietic stem cell transplantation that has a narrow therapeutic index, may cause various adverse reactions, including nephrotoxicity. This has a direct clinical impact on the patient. This study aims to summarize available evidence in the scientific literature on the use of cyclosporine in respect to its risk factor for the development of nephrotoxicity in patients submitted to hematopoietic stem cell transplantation. A systematic review was made with the following electronic databases: PubMed, Web of Science, Embase, Scopus, CINAHL, LILACS, SciELO and Cochrane BVS. The keywords used were: “bone marrow transplantation” OR “stem cell transplantation” OR “grafting, bone marrow” AND cyclosporine OR cyclosporin OR “risk factors” AND “acute kidney injury” OR “acute kidney injuries” OR “acute renal failure” OR “acute renal failures” OR “nephrotoxicity”. The level of scientific evidence of the studies was classified according to the Oxford Centre for Evidence Based Medicine. The final sample was composed of 19 studies, most of which (89.5%) had an observational design, evidence level 2B and pointed to an incidence of nephrotoxicity above 30%. The available evidence, considered as good quality and appropriate for the analyzed event, indicates that cyclosporine represents a risk factor for the occurrence of nephrotoxicity, particularly when combined with amphotericin B or aminoglycosides, agents commonly used in hematopoietic stem cell transplantation recipients.

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Introduction

Cyclosporine is an essential drug in the therapeutic regimen of allogeneic hematopoietic stem cell transplantation (HSCT)

recipients. It mainly acts on T cells, suppressing their activation and decreasing the release of lymphokines.^{1,2} On the other hand, cyclosporine administration demands systematic and regular serum level monitoring as, being a substrate of the cytochrome P450 enzyme system, it presents a narrow

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therapeutic index and is involved in drug interactions and relevant adverse reactions.^{3,4} The addition and/or interruption of other co-administered drugs may affect cyclosporine serum levels, since they may suppress or induce the cyclosporine metabolism or the metabolism of its metabolites, possibly causing ineffective therapy or increased toxicity, particularly nephrotoxicity.⁵

Although the epidemiology of nephrotoxicity in HSCT varies widely (from 14% to 73%), it is important due to the clinic impact of the resulting adverse effects.⁶⁻⁸ The variation in incidence can be explained by differences between studies regarding patient follow-up, type of conditioning regimen, the presence of hypertension prior to HSCT, hepatic sinusoidal obstruction syndrome, amphotericin B usage and other nephrotoxic drugs, as well as the differences in the criteria used for the definition of nephrotoxicity.⁹⁻¹¹ However, independent of risk factors, nephrotoxicity affects HSCT recipients, worsening their clinical condition.

Studies have shown that the nephrotoxicity in HSCT recipients represents a relevant risk factor for the development of chronic kidney injury. It has been associated with increases in both short-term and long-term mortality and may affect around 70% of patients.^{6,10} Considering the importance of cyclosporine for the success of HSCT, its nephrotoxic potential and the lack of studies that address this research question, the purpose of the current study was to accumulate the evidence available in the scientific literature about cyclosporine usage as a risk factor for the development of nephrotoxicity in HSCT recipients.

Method

A search for articles was performed with the following electronic databases: PubMed, Web of Science, Embase, Scopus, CINAHL, LILACS, SciELO and Cochrane BVS, without limits on time. Keyword selection was based on the PICO¹² strategy. Thus, the included keywords were "bone marrow transplantation" OR "stem cell transplantation" OR "grafting, bone marrow" for patient (P) AND "cyclosporine" OR "cyclosporin" OR "risk factors" for intervention (I) AND "acute kidney injury" OR "acute kidney injuries" OR "acute renal failure" OR "acute renal failures" OR "nephrotoxicity" for outcome (O).

The inclusion criteria of the study were: articles published in Portuguese, English or Spanish, with summaries available in databases, which referenced cyclosporine usage and nephrotoxicity in HSCT recipients. Studies concerning pediatric populations, editorials, letters and reviews were excluded. The systematic review was completed in December 2012.

Articles were selected by two authors separately and, in case of disagreement, a third author reviewed them to decide about inclusion. Upon searching, countless terms were observed related to nephrotoxicity, such as kidney toxicity, kidney dysfunction, acute renal failure (ARF) and acute kidney injury (AKI). In spite of AKI being the most commonly used term in recent studies, in this systematic review the term "nephrotoxicity" was considered more appropriate to analyze adverse drug events.

At the outset, 746 articles were found that were transferred to Endnote® Web.¹³ This program identified 184 duplicate articles, with 562 publications remaining. After reading the titles and abstracts, 518 articles were excluded. The remaining 44 articles were evaluated by reading in full and another 25 were excluded for the following reasons: two were histological studies and cyclosporine was not investigated as an independent variable of probable risk factor for nephrotoxicity in HSCT recipients in the other 23 articles.

Thus, 19 studies were included in this research and were summarized based on: the identification of the article, the database where it was found, the studied population, study design, patient characteristics, incidence of nephrotoxicity, intervention (cyclosporine, dosage, routes, usage time) and nephrotoxicity-related factors.

On reading the texts in full, the articles were evaluated using the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) technique.¹⁴ Although this is not a tool to evaluate the quality of an article's methodology, it presents important aspects regarding features of the methodology considered relevant for this research, which are: (A) context: place description, relevant dates including recruiting time, exposure, follow-up and collected data; (B) participants: eligibility criteria, selection method of participants; and (C) data source/measurement: data source and detailed evaluation methods. In cases where data were lacking, the article was excluded. The data on the articles were saved on a Microsoft Excel® worksheet and classified based on the level of scientific evidence, according to the Oxford Centre for Evidence Based Medicine.^{15,16}

Results

Most of the publications were identified in PubMed (84.2%) and presented an observational methodological design and non-probabilistic sample (89.5%) on patients undergoing HSCT, with follow-ups equal to or greater than 100 days (52.6%). All the studies presented level 2B scientific evidence.

The median age of subjects of the studies ranged from 18 to 52 years and the mean age was between 25 and 56.5 years. There was a predominance of myeloablative therapy (79%), and a diagnosis of leukemia (100%) or lymphoma (57.9%). More than half the studies (52.6%) presented the terms ARF or AKI to define nephrotoxicity, which are the predominant terms after 2000.

The cyclosporine dose varied from 2.5 to 5 mg/kg/day by intravenous administration, with a subsequent switch to peroral administration. The oral dose ranged from 5 to 12.5 mg/kg/day for three to six months. Most of the studies (89.5%) showed a greater than 30% incidence of nephrotoxicity and cyclosporine appeared as a risk factor for nephrotoxicity in around one-third of the studies (31.6%) associated with amphotericin B and/or aminoglycoside. Cyclosporine was used as an immunosuppressive agent monotherapy in 52.6% of the studies. In the others, it was associated with different immunosuppressants such as methotrexate, prednisone, cyclophosphamide and mycophenolate mofetil (Table 1).

Table 1 – Description of articles included in the systematic review.

Author (year)	Study type, follow-up and sample	Nephrotoxicity	
		Definition	Incidence Cyclosporine as a risk factor Other associated factors
Hows et al. (1983) ¹⁷	Cohort 4 weeks n = 33	Acute nephrotoxicity – serum Cr > 200 µmol/L	36.4% Statistically significant (p-value < 0.001) Associated with aminoglycoside
Kennedy et al. (1983) ¹⁸	RCT 90 days n = 47	Acute kidney toxicity – serum Cr ≥ 2× basal	80.0% Statistically significant (p-value < 0.01) Associated with amphotericin B
Kennedy et al. (1985) ¹⁹	Cohort 60 days n = 63	Kidney dysfunction – serum Cr ≥ 2× basal	86.0% Statistically significant (p-value < 0.001) Associated with amphotericin B
Kone et al. (1988) ²⁰	RCT Double blind 100 days n = 82	Kidney dysfunction – serum Cr elevated	64.0% Cyclosporine is the cause (descriptive analysis) Hypertension and associated with hypomagnesemia
Miller et al. (1994) ²¹	Cohort 4 weeks n = 45	Nephrotoxicity – serum Cr > 2 mg/dL	31.0% Statistically significant (p-value < 0.01) Associated with amphotericin B
Miralbell et al. (1996) ²²	Cohort – n = 79	Kidney dysfunction – serum Cr > 110 µmol/L	– Not significant
Parikh et al. (2002) ²³	Cohort 1 year n = 88	Kidney dysfunction – conventional criteria	92.0% Not significant
Kishi et al. (2005) ²⁴	Cohort 28 days n = 35	Kidney dysfunction – CTC	54.3% Not significant
Hingorani et al. (2005) ⁹	Cohort – n = 159	ARF – serum Cr ≥ 2× basal	36.0% Not significant
Caliskan et al. (2006) ²⁵	Cohort 100 days n = 47	AKI – Conventional criteria	70.0% Statistical significance (p = 0.04) Associated with aminoglycoside and amphotericin B (descriptive analysis)
Kersting et al. (2007) ¹⁰	Cohort 3 months n = 363	ARF – conventional criteria	93.4% Not significant
Lopes et al. (2008) ²⁶	Cohort 100 days n = 82	AKI – RIFLE	53.6% Cyclosporine is the cause (descriptive analysis)
Kersting et al. (2008) ²⁷	Cohort – n = 150	ARF – conventional criteria	94.0% Cyclosporine is the cause (descriptive analysis)
Mae et al. (2008) ²⁸	Cohort 100 days n = 54	AKI – serum Cr ≥ 2× basal	27.8% Not significant
Pinana et al. (2009) ²⁹	Cohort 1 year n = 188	ARF – conventional criteria	52.0% Cyclosporine is the cause (descriptive analysis)
Saddadi et al. (2010) ³⁰	Cohort 180 days n = 378	AKI – serum Cr ≥ 2× basal	37.6% Statistical significance (p-value < 0.001) Associated with amphotericin B
Kagoya et al. (2011) ³¹	Cohort 100 days n = 207	AKI – RIFLE	76.3% Cyclosporine is the cause (descriptive analysis)
Helal et al. (2011) ³²	Cohort 1 year n = 101	ARF – serum Cr ≥ 2× basal	57.4% Not significant
Bao et al. (2011) ³³	Cohort 100 days n = 143	AKI – RIFLE	48.9% Not significant

RCT: randomized clinical trials; Cr: creatinine; CTC: common toxicity criteria; ARF: acute renal failure; AKI: acute kidney injury; RIFLE: risk, injury, failure, loss and end-stage kidney disease.

Discussion

The evidence from this research suggests that cyclosporine represents a risk factor for the development of nephrotoxicity in HSCT recipients,^{17–19,21,25,30} in the context of continuous usage and increasing serum levels^{17,19} of cyclosporine,^{17–19,34} with the co-administration of amphotericin B^{18,19,21,25,30} and/or aminoglycoside antibiotics.^{17,25}

There was a predominance of cohort studies,^{9,10,17,19,21–33} which were classified according to their scientific evidence as level 2B. In other words, they are trustworthy and good quality studies; thus, it is highly unlikely that new studies can show substantial changes regarding effects.^{15,16} Although the observational methodological design does not represent the highest level of scientific evidence, it brings information about cyclosporine usage by different patient groups and analyzes, above all, the impact of long-term immunosuppression,

proposing important findings on events of toxicity, especially those at low frequency that are not typically identified in clinical trials.

In general, patient follow-ups were greater than or equal to 100 days.^{20,23,25,26,28-33} This is expected since these patients generally present risks for acute complications and mortality within this time frame. Moreover, the literature suggests that the first 100 days post-transplant is a "cut off" for the occurrence of nephrotoxicity,^{6,35} the object of analysis in this systematic review.

More than half (52.6%) of the included papers used ARF or AKI to define nephrotoxicity. As mentioned, these terms became predominant after 2000. The variety of terms for defining nephrotoxicity can be explained by the addition of different diagnostic criteria in 1980. One criterion of nephrotoxicity that has become common is serum creatinine level equal to or greater than double the patient's baseline value.^{9,17,19,21,30,32,36}

The predominant conditioning regimen was myeloablative (79%), the intensity of which causes total or almost total bone marrow cell destruction in the recipient, in general, through high doses of chemotherapy.³⁷ Patients undergoing myeloablative conditioning, on the whole, presented a mean or median age under 50 years and the regimen was not an independent variable for nephrotoxicity.

Almost all studies (89.5%) indicated an incidence of nephrotoxicity of more than 30%.^{9,10,17-21,23-27,29-33} In other words, nearly one-third of patients undergoing HSCT and exposed to cyclosporine at doses from 5.0 to 12.5 mg/kg/day by oral administration developed some sort of kidney dysfunction. Cyclosporine was considered a risk factor for nephrotoxicity in 31.6% of the investigations.^{17-19,21,25,30}

In the studies which indicated some association between cyclosporine and nephrotoxicity, synergism between different nephrotoxic agents – cyclosporine, amphotericin B and/or aminoglycosides – was observed.^{17-19,21,25,30} The complex pharmacotherapy in patients undergoing HSCT, which includes not only a large number of drugs with interactive potential, but also combinations of agents with similar adverse reaction profiles, enhances the toxic effects.^{19,21,25,30,38} In this case, it is well known that cyclosporine, aminoglycosides and amphotericin B may cause acute tubular necrosis. This dysfunction can appear in patients undergoing monotherapy, but, overall, it is worsened by these combinations (toxic synergism).³⁹

The studies indicate a correlation between nephrotoxicity and increased serum creatinine levels as well as cyclosporine level.^{17,18} One of them clearly demonstrated a correlation between serum levels of cyclosporine, creatinine and urea (p -value < 0.001); in one fraction of the sample, the rise in serum cyclosporine preceded an increase in creatinine. Another risk factor for acute nephrotoxicity with cyclosporine therapy was the simultaneous use of aminoglycoside antibiotics (p -value = 0.01). Cyclosporine levels of less than 400 ng/mL were not seen to cause serious acute nephrotoxicity.¹⁷

Another investigation compared a group of patients who simultaneously took methotrexate and amphotericin B with another group concurrently taking cyclosporine and amphotericin B; the group treated with cyclosporine presented a

higher incidence of nephrotoxicity (80%) than the group treated with methotrexate (19%) (p -value < 0.01).¹⁸

The cyclosporine concentrations used were associated with nephrotoxicity in patients undergoing myeloablative therapy. The concentrations varied from <150 ng/mL to >250 ng/mL; furthermore, when patients presented a serum cyclosporine concentration higher than 250 ng/mL, the development of toxicity was faster. These differences related to cyclosporine concentration were not explained by risk factors such as age, basal creatinine or concurrent use of nephrotoxic antibiotics. It was ascertained that the highest mean concentration of cyclosporine was associated with the highest risk for the development of nephrotoxicity (p -value < 0.001). In addition, comparing patients who took amphotericin B with those who had not taken this antifungal, stratified by cyclosporine concentration, showed that this drug was a significant independent risk factor for the development of nephrotoxicity (p -value < 0.01).¹⁹

In allogeneic bone marrow transplant recipients, cyclosporine represented the most frequent cause of nephrotoxicity. However, the authors did not observe a correlation between a short period of elevated cyclosporine concentration and creatinine clearance over a period of 20 days post-transplant. Nephrotoxicity was more frequent with myeloablative allogeneic (91%) than with autologous transplantation (52%) (p -value = 0.004). Those differences were attributed to graft-versus-host disease and immunosuppressive drug usage, including the toxicity caused by cyclosporine.²⁵ Comparing kidney dysfunction patients to those with regular kidney function, a univariate analysis did not indicate statistically significant differences concerning aminoglycoside or amphotericin B use. Nonetheless, in the descriptive analysis, amphotericin B contributed to nephrotoxicity in the group undergoing allogeneic HSCT (5%). In the group of autologous HSCT, amphotericin B (31%) and aminoglycoside (8%) use contributed to nephrotoxicity.²⁵

In other studies, authors found that cyclosporine causes significant dose-dependent toxicity (relative risk: 6.17; 95% confidence: 4.03–9.43; p -value < 0.001). In a descriptive analysis, aminoglycoside (amikacin) and amphotericin B use were related to 14.2% and 10.3% of instances of nephrotoxicity, respectively.³⁰

Some studies considered cyclosporine a cause of nephrotoxicity based on descriptive analysis.^{20,25,26,28,31} One of these studies in particular indicated that cyclosporine was responsible for 21% of grade 2 nephrotoxicity cases.²⁷

The present systematic review was limited due to lack of detailed information from primary studies, especially about agent exposure (cyclosporine): biochemical methods used to dose cyclosporine, the time interval between the last administration of cyclosporine and blood collection for serum dosage of the immunosuppressive drug, the type of biological sample used to dose the drug, as well as the routes and time of cyclosporine administration. These data could support further analysis. The nephrotoxicity valuation parameters, as well as their definition, were quite variable. Furthermore, almost one-third of the studies used descriptive analysis. Hence, in spite of a wide and systematic search, the possibility of bias should not be excluded.

Contribution to the clinical context

Some of the studies in this systematic review considered that nephrotoxicity can be prevented by a measure of caution during the use of cyclosporine associated with amphotericin B or aminoglycosides in the form of careful administration and kidney function monitoring.^{18,20,21} Another study³² recommended that early identification of risk factors for AKI, would avoid, whenever possible, the exposure of more susceptible patients to nephrotoxic drugs during follow-up.²⁹ The risk, injury, failure, loss, end-stage kidney disease (RIFLE) criteria were considered an important tool to stratify HSCT recipients in relation to risk of death.^{33,40} In a previous study, these diagnostic criteria presented good sensitivity on the evaluation of nephrotoxicity.

Conclusion

The incidence of nephrotoxicity following allogeneic HSCT ranged from 27.8% to 94% with cyclosporine being considered a risk factor for this adverse event in one-third of the studies. Some studies, which show an association between cyclosporine and nephrotoxicity, have found synergism with other nephrotoxic drugs such as amphotericin B and aminoglycoside. Systematic monitoring of serum levels of the administered drugs and monitoring of the patient's kidney function are essential. In addition, it is indispensable to avoid, whenever possible, the association of cyclosporine with other nephrotoxic drugs. Furthermore, it is necessary to investigate possible risk factors for nephrotoxicity in each HSCT recipient. Finally, considering the importance of cyclosporine to the success of HSCT and that nephrotoxicity in HSCT recipients has been associated with increased mortality, this issue requires particular attention.

Conflict of interest

The authors declare no conflicts of interest.

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